

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to "Commissioner for Patents, Mail Stop PCT, P.O. Box 1450, Alexandria, VA 22313-1450" June 26, 2003.

10/502074

Harold Hull
Name of person mailing document

Harold Hull
Signature

DT12 Rec'd PCT/PTO 19 JUL 2004
June 26, 2003
Date

IN THE UNITED STATES RECEIVING OFFICE (RO/US)

APPLICANTS : YALE UNIVERSITY; UNIVERSITY OF TENNESSEE
RESEARCH FOUNDATION; BAKER, David C.; CHENG, Yung-
Chi; and ZHONG, Sanbao

INT'L APPLICATION NO. : PCT/US03/04072

INT'L FILING DATE : 12 February 2003 (12.02.2003)

TITLE : NOVEL TYLOINDICINES AND RELATED PROCESSES,
PHARMACEUTICAL COMPOSITIONS AND METHODS

Commissioner for Patents
Mail Stop PCT
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF SUBSTITUTE REQUEST FORM SHEET

S I R:

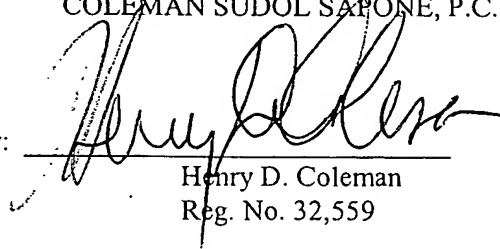
Applicant, THE UNIVERSITY OF TENNESSEE RESEARCH CORPORATION, recently changed its name to UNIVERSITY OF TENNESSEE RESEARCH FOUNDATION. Accordingly, a copy of the document associated with such name change from the Department of State of the State of Tennessee, U.S.A. is enclosed.

Enclosed herewith please find a substitute first sheet of the PCT Request form. Please replace the incorrect first sheet of the Request with the enclosed first sheet.

Respectfully submitted,
COLEMAN SUDOL SAPONE, P.C.

Dated: June 26, 2003

By:


Henry D. Coleman
Reg. No. 32,559

714 Colorado Avenue
Bridgeport, CT 06605-1601
(203) 366-3560

PCT REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference:
(if desired)(12 characters maximum)

Y03-069

Box No. I TITLE OF INVENTION

NOVEL TYLOINDICINES AND RELATED PROCESSES, PHARMACEUTICAL COMPOSITIONS AND METHODS

Box No. II APPLICANT

Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

Yale University
Two Whitney Avenue
New Haven, Connecticut 06511
United States of America

☐ This person is also inventor

Telephone No.
(203) 432-5546

Facsimile No.
203) 432-5449

Teleprinter No.

State (i.e. country) of Nationality: US

State (i.e. country) of Residence: US

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the states indicated in the supplemental box

Box No. III FURTHER APPLICANT(S) AND/OR FURTHER INVENTOR(S)

Name and address: (family name followed by given name; for a legal entity, full official Designation. The address must include postal code and name of country)

University of Tennessee Research Foundation
1534 White Avenue, Suite 403
Knoxville, TN 37996
United States of America

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only (if this check-box is marked, do not fill in below)

State (i.e. country) of nationality: US

State (i.e. country) of residence: US

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the states indicated in the supplemental box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (family name followed by given name; for a legal entity, full official Designation. The address must include postal code and name of country)

Henry D. Coleman
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
United States of America

Telephone No. (203) 366-3560

Facsimile No. (203) 335-6779

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.



I, RILEY C. DARNELL, Secretary of State of the State of Tennessee, do hereby
certify that the Articles of Amendment to the Charter of

THE UNIVERSITY OF TENNESSEE RESEARCH CORPORATION

were filed in this office on April 3, 2003, changing the name to:

UNIVERSITY OF TENNESSEE RESEARCH FOUNDATION



In Witness Whereof, I have hereto affixed my
signature and the Great Seal of the State, at
Nashville, this 14TH day of May
In the year of our Lord two thousand three

Riley C. Darnell

Secretary of State

by Deborah S. Chaney



UNITED STATES
PATENT AND
TRADEMARK OFFICE

RECEIVED

OCT 27 2003

OCTOBER 23, 2003

PTAS

COLEMAN SUDOL SAPONE, P.C.
C/O HENRY D. COLEMAN
714 COLORADO AVENUE
BRIDGEPORT, CONNECTICUT 06605

COLEMAN SUDOL SAPONE, P.C.
Chief Financial Officer and Chief Administrative Officer
Washington, DC 20231
www.uspto.gov



102451515A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 05/13/2003

REEL/FRAME: 014068/0212

NUMBER OF PAGES: 5

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

BAKER, DAVID C.

DOC DATE: 04/22/2003

ASSIGNOR:

ZHONG, SANBAO

DOC DATE: 04/29/2003

ASSIGNEE:

TENNESSEE RESEARCH CORPORATION,
UNIVERSITY OF, THE
1534 WHITE AVENUE, SUITE 403
KNOXVILLE, TENNESSEE 37996-1527

SERIAL NUMBER:

PATENT NUMBER:

PCT NUMBER: US0304072

FILING DATE:

ISSUE DATE:

014068/0212 PAGE 2

ALLYSON PURNELL, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS



UNITED STATES
PATENT AND
TRADEMARK OFFICE

RECEIVED

OCT 27 2003

COLEMAN SUDOL SAPONE, P.C.

OCTOBER 23, 2003

PTAS

Chief Financial Officer and Chief Administrative Officer
Washington, DC 20231
www.uspto.gov

COLEMAN SUDOL SAPONE, P.C.
HENRY D. COLEMAN
714 COLORADO AVENUE
BRIDGEPORT, CT 06605



102451516A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 05/13/2003

REEL/FRAME: 014068/0198

NUMBER OF PAGES: 5

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

CHENG, YUNG-CHI

DOC DATE: 04/21/2003

ASSIGNEE:

YALE UNIVERSITY
2 WHITNEY AVENUE
NEW HAVEN, CONNECTICUT 06511

SERIAL NUMBER:

PATENT NUMBER:

PCT NUMBER: US0304072

FILING DATE:

ISSUE DATE:

ANTIONE ROYALL, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

JUN 01 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

COLEMAN SUDOL SAPONE, P.C.

To:
HENRY D. COLEMAN
COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGEPORT, CT 06605-1601

PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

28 MAY 2004

Applicant's or agent's file reference

Y03-069

IMPORTANT NOTIFICATION

International application No.

PCT/US03/04072

International filing date (day/month/year)

12 February 2003 (12.02.2003)

Priority date (day/month/year)

15 February 2002 (15.02.2002)

Applicant

YALE UNIVERSITY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Patricia Bell-Harris
Evelyn Huang

Telephone No. 571/272-1600

Form PCT/IPEA/416 (July 1992)

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Y03-069		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US03/04072	International filing date (day/month/year) 12 February 2003 (12.02.2003)	Priority date (day/month/year) 15 February 2002 (15.02.2002)	
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/437, 31/4375, 31/4745, 31/55; C07D 455/03, 471/04; A61P 35/00, 29/00, 37/00 and US Cl.: 514/299, 306, 280, 283, 212.05; 546/112, 138, 183, 42, 58; 540/519, 576			
Applicant YALE UNIVERSITY			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 19 August 2003 (19.08.2003)		Date of completion of this report 10 May 2004 (10.05.2004)	
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230		Authorized officer <i>Valerie Bell-Harris</i> Evelyn Huang Telephone No. 571/272-1600	

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-44 as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____.
- ☒ the claims:
pages 45-63 as originally filed
pages NONE as amended (together with any statement) under Article 19
pages NONE filed with the demand
pages NONE filed with the letter of _____.
- ☒ the drawings:
pages 1-27 as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____.
- ☐ the sequence listing part of the description:
pages NONE as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims <u>2-25, 27, 29, 31, 55-58</u>	YES
	Claims <u>1, 26, 28, 30, 32-54, 59-62</u>	NO
Inventive Step (IS)	Claims <u>2-25, 27, 29, 31, 55-58</u>	YES
	Claims <u>1, 26, 28, 30, 32-54, 59-62</u>	NO
Industrial Applicability (IA)	Claims <u>1-62</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by TRIGO et al. The compounds 5, 6, 7 wherein R is methoxy (page 69, Scheme 1), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by PATON et al. The compounds I, II, VI (page 1309), VII, VIII, IX (page 1310), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by PETTIT et al. The compounds 1a-b, 2, 3, 4a-c (page 915), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by LIEPA et al. The compounds 12, 13, 14 (page 827), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by OHYAMA et al. The compounds I, II (page 164), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by SAIFAH et al. The compounds 1, 2, 6a-c (page 354), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by KRMPOTIC et al. The compounds II, III (page 1508), the composition and method of use thereof, are encompassed by the instant claims.

Claims 2-25, 27, 29, 31, 55-58 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the instant compound having the specific substituents.

Claims 1-62 meet the criteria set out in PCT Article 33(4), and thus find industrial applicability because the subject matter claimed can be made or used in the pharmaceutical industry for treating neoplasia or cancer.

----- NEW CITATIONS -----

FEB 1 2004

PATENT COOPERATION TREATY

COLEMAN SUDOL SAPONE, P.C.

PCT

From the INTERNATIONAL BUREAU

To:

COLEMAN, Henry, D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
United States of America

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year) 29 January 2004 (29.01.2004)		
Applicant's or agent's file reference Y03-069		IMPORTANT INFORMATION
International application No. PCT/US2003/004072	International filing date (day/month/year) 12 February 2003 (12.02.2003)	
Priority date (day/month/year) 15 February 2002 (15.02.2002)		
Applicant YALE UNIVERSITY et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,
SK, TR

National : BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC,
EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SD, SE, SG, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU,
ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 338.89.75</p>	<p>Authorized officer: Rosana REYES (Fax : 338 89 75)</p> <p>Telephone No. (41-22) 338 8471</p>
---	--

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED
FEB 11 2004
COLEMAN SUDOL SAPONE, P.C.

PCT

WRITTEN OPINION

(PCT Rule 66)

To:
HENRY D. COLEMAN
COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGEPORT, CT 06605-1601

Date of Mailing (day/month/year) **10 FEB 2004**

Applicant's or agent's file reference

Y03-069

REPLY DUE

within 2 months/days from
the above date of mailing

International application No.

PCT/US03/04072

International filing date (day/month/year)

12 February 2003 (12.02.2003)

Priority date (day/month/year)

15 February 2002 (15.02.2002)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 31/437, 31/4375, 31/4745, 31/55; C07D 455/03, 471/04; A61P 35/00, 29/00, 37/00 and US Cl.: 514/299, 306, 280, 283, 212.05; 546/112, 138, 183, 42, 58; 540/519, 576

Applicant

YALE UNIVERSITY

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 15 June 2004 (15.06.2004).

Name and mailing address of the IPEA/US

Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer:

Valerie Bell-Harris for
Evelyn Huang

Telephone No. 703-308-1235

WRITTEN OPINION

International application No.

PCT/US03/0

I. Basis of the opinion

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
 pages 1-44, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☒ the claims:
 pages 45-63, as originally filed
 pages NONE, as amended (together with any statement) under Article 19
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☒ the drawings:
 pages 1-27, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☐ the sequence listing part of the description:
 pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>2-25, 27, 29, 31, 55-58</u>	YES
	Claims <u>1, 26, 28, 30, 32-54, 59-62</u>	NO
Inventive Step (IS)	Claims <u>2-25, 27, 29, 31, 55-58</u>	YES
	Claims <u>1, 26, 28, 30, 32-54, 59-62</u>	NO
Industrial Applicability (IA)	Claims <u>1-62</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by TRIGO et al. The compounds 5, 6, 7 wherein R is methoxy (page 69, Scheme 1), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by PATON et al. The compounds I, II, VI (page 1309), VII, VIII, IX (page 1310), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by PETTIT et al. The compounds 1a-b, 2, 3, 4a-c (page 915), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by LIEPA et al. The compounds 12, 13, 14 (page 827), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by OHYAMA et al. The compounds I, II (page 164), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by SAIFAH et al. The compounds 1; 2, 6a-c (page 354), the composition and method of use thereof, are encompassed by the instant claims.

Claims 1, 26, 28, 30, 2-54, and 59-62 lack novelty under PCT Article 33(2) as being anticipated by KRMPOTIC et al. The compounds II, III (page 1508), the composition and method of use thereof, are encompassed by the instant claims.

Claims 2-25, 27, 29, 31, 55-58 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the instant compound having the specific substituents.

Claims 1-62 meet the criteria set out in PCT Article 33(4), and thus find industrial applicability because the subject matter claimed can be made or used in the pharmaceutical industry for treating neoplasia or cancer.

----- NEW CITATIONS -----

WRITTEN OPINION

International application No.
PCT/US02/072

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

PC

From the INTERNATIONAL BUREAU

To:

COLEMAN, Henry, D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
ETATS-UNIS D'AMERIQUE

RECEIVED

JAN 20 2004

COLEMAN SUDOL SAPONE, P.C.

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
28 August 2003 (28.08.2003)

PCT

(10) International Publication Number
WO 2003/070166 A3

(51) International Patent Classification⁷: **A61K 31/437**,
31/4375, 31/4745, 31/55, C07D 455/03, 471/04, A61P
35/00, 29/00, 37/00

(74) Agent: COLEMAN, Henry, D.; Coleman Sudol Sapone,
P.C., 714 Colorado Avenue, Bridgeport, CT 06605-1601
(US).

(21) International Application Number:
PCT/US2003/004072

(22) International Filing Date: 12 February 2003 (12.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/357,354 15 February 2002 (15.02.2002) US

(71) Applicants (*for all designated States except US*): YALE
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Haven, CT 06511 (US). UNIVERSITY OF TEN-
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Redcliffe Avenue, Apt. 2A, Highland Park, NJ 08904 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,
SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
8 January 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL TYLOINDICINES AND RELATED PROCESSES, PHARMACEUTICAL COMPOSITIONS AND METHODS

(57) Abstract: The invention provides novel tyloindicine analogues and related processes, pharmaceutical compositions, and methods. The novel tyloindicines are useful in a wide variety of antiviral, antineoplastic, antibacterial, and anti-inflammatory applications. Preferred embodiments of the instant invention include the novel tyloindicine designated herein as compound IT-3 (NSC-716802). Compounds of the instant invention have exhibited potent antiviral and anticancer activity *in vitro*. The invention further provides novel methods of treating neoplastic, bacterial, viral, and anti-inflammatory disorders using tyloindicines including the novel tyloindicine analogues of the instant invention. The invention also provides novel syntheses of tyloindicines including the novel tyloindicines analogues of the instant invention.



WO 2003/070166 A3

INTERNATIONAL SEARCH REPORT

PCT/US03/04072

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRMPOTIC et al. Cryptopleurine, an active antiviral alkaloid from <i>Boehmeria cylindrica</i> (L.) Sw.(Urticaceae). <i>Journal of Pharmaceutical Sciences</i> . September 1972, Vol. 61, No. 9, pages 1508-1509, especially page 1508.	1,26,28,30,32-54,59-62

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/04072

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/437, 31/4375, 31/4745, 31/55; C07D 455/03, 471/04; A61P 35/00, 29/00, 37/00
US CL : 514/299, 306, 280, 283, 212.05; 546/112, 138, 183, 42, 58; 540/519, 576

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/299, 306, 280, 283, 212.05; 546/112, 138, 183, 42, 58; 540/519, 576

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TRIGO et al. Contribution to the synthesis of Cryptopleurine and related phenanthroquinolizidines. J. Heterocyclic Chem. January 1980, Vol. 17, pages 69-72, especially page 69, Scheme 1, compounds 5, 6, 7.	1, 26, 28, 30, 32-54, 59-62
X	PATON et al. Cryptopleurine, a synthesis based on biogenetic considerations. J. Chem. Soc. (C), 1969, Vol. 10, pages 1309-1314, especially page 1309 and page 1310.	1, 26, 28, 30, 32-54, 59-62
X	PETTIT et al. Antineoplastic agents, 103. The isolation and structure of hypostetastins 1 and 2 from the East African Hypostetes Verticillaris. J. Natural Products. November-December 1984, Vol. 47, No. 6, pages 913-919, especially page 913.	1, 26, 28, 30, 32-54, 59-62
X	LIEPA et al. An improved phenanthrene synthesis: a simple route to Tylophorine. J.C.S. Chem. Comm. 1977, Vol. 22, pages 826-827, especially page 827, Scheme 2.	1, 26, 28, 30, 32-54, 59-62
X	OHYAMA et al. Cytotoxic phenanthroquinolizidine alkaloids in Tylophora tanakae against human gastric carcinoma cells. Proc. Japan Acad. Ser. B. 2000, Vol. 76B, No. 10, pages 161-165, especially page 164.	1, 26, 28, 30, 32-54, 59-62
X	SAIFAH et al. Constituents of the leaves of Cissus Rheifolia. J. Natural Products. May-June 1983, Vol. 46, No. 3, pages 353-358, especially page 354..	1, 26, 28, 30, 32-54, 59-62



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

09 May 2003 (09.05.2003)

Date of mailing of the international search report

20 OCT 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Evelyn Huang
Telephone No. 703-308-1235

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED

DEC 11 2003

COLEMAN SUDOL SAPONE, P.C.
PCT

To:

HENRY D. COLEMAN
COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGEPORT, CONNECTICUT 06605-1601

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

08 DEC 2003

Applicant's or agent's file reference

Y03-069

IMPORTANT NOTIFICATION

International application No.

PCT/US03/04072

International filing date (day/month/year)

12 Feb 2003

Priority date (day/month/year)

15 Feb 2002

Applicant

YALE UNIVERSITY

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

19 Aug 2003

2. That date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 703-305-3230

Form PCT/IPEA/402 (July 1998)

Authorized officer

Valerie Jackson

Telephone No. 703-305-3756

PATENT COOPERATION TREATY OCT 22 2003

From the INTERNATIONAL SEARCHING AUTHORITY

COLEMAN SUDOL SAPONE, P.C.

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To: HENRY D. COLEMAN COLEMAN SUDOL SAPONE, P.C. 714 COLORADO AVENUE BRIDGEPORT, CT 06605-1601	Date of Mailing (day/month/year)
Applicant's or agent's file reference Y03-069	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US03/04072	International filing date (day/month/year) 12 February 2003 (12.02.2003)
Applicant YALE UNIVERSITY	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Evelyn Huang Telephone No. 703-308-1235
--	--

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
HENRY D. COLEMAN
COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGEPORT, CT 06605-1601

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference Y03-069	Date of Mailing (day/month/year) 20 OCT 2003
International application No. PCT/US03/04072	International filing date (day/month/year) 12 February 2003 (12.02.2003)
Applicant YALE UNIVERSITY	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer

Valerie Bell-Harris for
Evelyn Huang

Telephone No. 703-308-1235

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference Y03-069	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/04072	International filing date (<i>day/month/year</i>) 12 February 2003 (12.02.2003)	(Earliest) Priority Date (<i>day/month/year</i>) 15 February 2002 (15.02.2002)
Applicant YALE UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐

contained in the international application in written form.

☐

filed together with the international application in computer readable form.

☐

furnished subsequently to this Authority in written form.

☐

furnished subsequently to this Authority in computer readable form.

☐

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the **title**,

☒

the text is approved as submitted by the applicant.

☐

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒

the text is approved as submitted by the applicant.

☐

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐

as suggested by the applicant.

☐

because the applicant failed to suggest a figure.

☐

because this figure better characterizes the invention.

☒

None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/04072

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/437, 31/4375, 31/4745, 31/55; C07D 455/03, 471/04; A61P 35/00, 29/00, 37/00

US CL : 514/299, 306, 280, 283, 212.05; 546/112, 138, 183, 42, 58; 540/519, 576

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/299, 306, 280, 283, 212.05; 546/112, 138, 183, 42, 58; 540/519, 576

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TRIGO et al. Contribution to the synthesis of Cryptopleurine and related phenanthroquinolizidines. J. Heterocyclic Chem. January 1980, Vol. 17, pages 69-72, especially page 69, Scheme 1, compounds 5, 6, 7.	1, 26, 28, 30, 32-54, 59-62
X	PATON et al. Cryptopleurine, a synthesis based on biogenetic considerations. J. Chem. Soc. (C), 1969, Vol. 10, pages 1309-1314, especially page 1309 and page 1310.	1, 26, 28, 30, 32-54, 59-62
X	PETTIT et al. Antineoplastic agents, 103. The isolation and structure of hypostestastins 1 and 2 from the East African Hyposetes Verticillaris. J. Natural Products. November-December 1984, Vol. 47, No. 6, pages 913-919, especially page 913.	1, 26, 28, 30, 32-54, 59-62
X	LIEPA et al. An improved phenanthrene synthesis: a simple route to Tylophorine. J.C.S. Chem. Comm. 1977, Vol. 22, pages 826-827, especially page 827, Scheme 2.	1, 26, 28, 30, 32-54, 59-62
X	OHYAMA et al. Cytotoxic phenanthroquinolizidine alkaloids in Tylophora tanakae against human gastric carcinoma cells. Proc. Japan Acad. Ser. B. 2000, Vol. 76B, No. 10, pages 161-165, especially page 164.	1, 26, 28, 30, 32-54, 59-62
X	SAIFAH et al. Constituents of the leaves of Cissus Rheifolia. J. Natural Products. May-June 1983, Vol. 46, No. 3, pages 353-358, especially page 354..	1, 26, 28, 30, 32-54, 59-62



Further documents are listed in the continuation of Box C.



See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 09 May 2003 (09.05.2003)	Date of mailing of the international search report 20 OCT 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Valerie Bell-Harms for Evelyn Huang Telephone No. 703-308-1235

INTERNATIONAL SEARCH REPORT

PCT/US03/04072

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRMPOTIC et al. Cryptopleurine, an active antiviral alkaloid from <i>Boehmeria cylindrica</i> (L.) Sw.(Urticaceae). Journal of Pharmaceutical Sciences. September 1972, Vol. 61, No. 9, pages 1508-1509, especially page 1508.	1,26,28,30,32-54,59-62

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PCTNOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

RECEIVED
SEP 10 2003COLEMAN, Henry, D
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
ETATS-UNIS D'AMERIQUE

Date of mailing(day/month/year) 28 August 2003 (28.08.03)		
Applicant's or agent's file reference Y03-069		IMPORTANT NOTICE
International application No. PCT/US03/04072	International filing date(day/month/year) 12 February 2003 (12.02.03)	
		Priority date(day/month/year) 15 February 2002 (15.02.02)
Applicant YALE UNIVERSITY, et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DE, DZ, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NO, NZ, OA, OM, PH, PL, PT, RO, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 28 August 2003 (28.08.03) under No. 03/070166

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Judith Zahra
Facsimile No.(41-22) 740.14.35 PCT/18/308	Telephone No.(41-22) 338.91.11

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 August 2003 (28.08.2003)

PCT

(10) International Publication Number
WO 03/070166 A2

(51) International Patent Classification⁷: **A61K**

(21) International Application Number: **PCT/US03/04072**

(22) International Filing Date: 12 February 2003 (12.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/357,354 15 February 2002 (15.02.2002) US

(71) Applicants (*for all designated States except US*): **YALE UNIVERSITY** [US/US]; Two Whitney Avenue, New Haven, CT 06511 (US). **UNIVERSITY OF TENNESSEE RESEARCH CORPORATION** [US/US]; 1534 White Avenue, Suite 403, Knoxville, TN 37996 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BAKER, David, C.** [US/US]; 5708 Glen Cove Dr., Knoxville, TN 37919 (US). **CHENG, Yung-Chi** [US/US]; 961 Baldwin Rd., Woodbridge, CT 06525 (US). **ZHONG, Sanbao** [CN/US]; 18 Redcliffe Avenue, Apt. 2A, Highland Park, NJ 08904 (US).

(74) Agent: **COLEMAN, Henry, D.**; Coleman Sudol Sapone, P.C., 714 Colorado Avenue, Bridgeport, CT 06605-1601 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL TYLOINDICINES AND RELATED PROCESSES, PHARMACEUTICAL COMPOSITIONS AND METHODS

(57) Abstract: The invention provides novel tyloindicine analogues and related processes, pharmaceutical compositions, and methods. The novel tyloindicines are useful in a wide variety of antiviral, antineoplastic, antibacterial, and anti-inflammatory applications. Preferred embodiments of the instant invention include the novel tyloindicine designated herein as compound IT-3 (NSC-716802). Compounds of the instant invention have exhibited potent antiviral and anticancer activity *in vitro*. The invention further provides novel methods of treating neoplastic, bacterial, viral, and anti-inflammatory disorders using tyloindicines including the novel tyloindicine analogues of the instant invention. The invention also provides novel syntheses of tyloindicines including the novel tyloindicine analogues of the instant invention.

WO 03/070166 A2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS : Yale University et al.
INT'L APPL'N NO. : PCT/US03/04072
INT'L FILING DATE : 12 February 2003
FOR : Novel Tyloindicines and Related Processes, Pharmaceutical
Compositions and Methods
ATT'Y DOCKET NO. : Y03-069

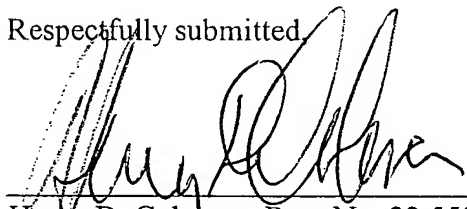
Commissioner for Patents
Mail Stop PCT
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTED HERewith ARE THE FOLLOWING:

X PCT Demand (4 sheets)
X Fee Calculation Sheet
X Check for \$636.00

Dated: 8/19/03

Respectfully submitted,


Henry D. Coleman, Reg. No. 32,559
COLEMAN SUDOL SAPONE, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
Tel. (203) 366-3560

EXPRESS MAIL No. EV 332298589 US

Date of Deposit: August 19, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to:
Commissioner for Patents, Mail Stop PCT, P.O. Box 1450, Alexandria, VA 22313-1450

Harold Hull
Name of person mailing document

Signature

August 19, 2003
Date

competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/_____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use
only

Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference Y03-069
International application No. PCT/US03/04072	International filing date 12 February 2003 (12.02.03)	(Earliest) Priority date (day/month/year) 15 February 2002 (15.02.02)
Title of invention: NOVEL TYLOINDICINES AND RELATED PROCESSES, PHARMACEUTICAL COMPOSITIONS AND METHODS		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Yale University Two Whitney Avenue New Haven, Connecticut 06511 United States of America		Telephone No.: 203-432-5546
		Facsimile No.: 203-432-5449
		Teleprinter No.:
State (that is country) of nationality: US		State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) University of Tennessee Research Foundation 1534 White Avenue, Suite 403 Knoxville, Tennessee 37996 United States of America		
State (that is, country) of nationality: US		State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BAKER, David C. 5708 Glen Cove Drive Knoxville, Tennessee 37919 United States of America		
State (that is, country) of nationality: US		State (that is, country) of residence: US
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.		

If none of the following sub-boxes is used, this sheet is not to be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

CHENG, Yung-Chi
961 Baldwin Road
Woodbridge, Connecticut 06525
United States of America

State (that is, country) of nationality: US

State (that is, country) of residence: US

Name and address: (Family name followed by given name; for a legal entity, full official designation.. The address must include postal code and name of country.)

ZHONG, Sanbao
18 Redcliffe Avenue, Apt. 2A
Highland Park, New Jersey 08904
United States of America

State (that is, country) of nationality: CN

State (that is, country) of residence: US

Name and address: (Family name followed by given name; for a legal entity, full official designation.. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on a continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(family name followed by given name; for a legal entity, full official designation.**The address must include postal code and name of country.)*COLEMAN, Henry D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
United States of America

Telephone No.

(203) 366-3560

Facsimile No.

(203) 335-6779

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed
☐ as amended under Article 34the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34the drawings ☐ as originally filed
☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination:

...English.....

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purpose of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT),*

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Bo No. IV, for the purpose of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (<i>specify</i>) | : | sheets |

For International Preliminary
Examining Authority use only

received	not received
----------	--------------

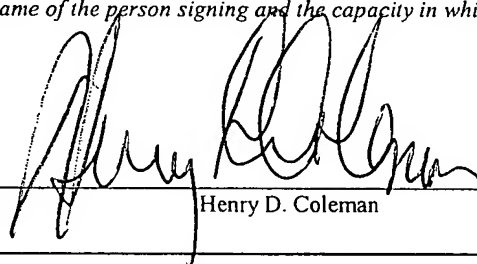
- | | |
|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. <input checked="" type="checkbox"/> fee calculation sheet | 4. <input type="checkbox"/> statement explaining lack of signature |
| 2. <input type="checkbox"/> separate signed power of attorney | 5. <input type="checkbox"/> Nucleotide an or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 6. <input type="checkbox"/> other (<i>specify</i>): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



Henry D. Coleman

For International Preliminary Examining Authority use
only

1. Date of actual receipt of
DEMAND:

2. Adjusted date of receipt of demand due
to CORRECTIONS under Rule 60.1(b):

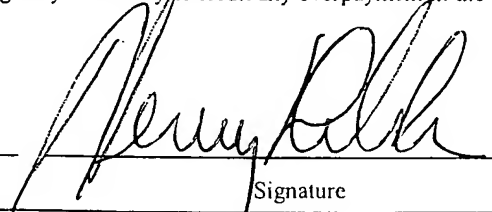
- | | |
|--|---|
| 3. <input type="checkbox"/> The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply | <input type="checkbox"/> The applicant has been informed accordingly. |
| 4. <input type="checkbox"/> The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. <input type="checkbox"/> Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

Demand received from IPEA on:

For International Bureau use
only

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/US03/04072 <hr/> Applicant's or agent's file reference Y03-069	For International Preliminary Examining Authority use only <hr/> Date stamp of the IPEA
Applicant: Yale University Calculation of prescribed fees: 1. Preliminary examination fee \$490.00 P <hr style="width: 20%; margin-left: auto; margin-right: 0;"/> 2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>) \$146.00 H <hr style="width: 20%; margin-left: auto; margin-right: 0;"/> 3. Total of prescribed fees. Add the amounts entered at P and H and enter total in the TOTAL box <div style="text-align: right; border: 1px solid black; padding: 5px; width: 150px; margin: 10px auto;">\$636.00</div> <div style="text-align: right; margin-top: 5px;">TOTAL</div>	
Mode of Payment <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> authorization to charge deposit account with IPEA (see below) </div> <div> <input type="checkbox"/> cash </div> </div> <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> cheque </div> <div> <input type="checkbox"/> revenue stamps </div> </div> <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> postal money order </div> <div> <input type="checkbox"/> coupons </div> </div> <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> bank draft </div> <div> <input type="checkbox"/> other (specify): </div> </div>	
Deposit Account Authorization (<i>this mode of payment may not be available at all IPEAs</i>) The IPEA/ US <input type="checkbox"/> is hereby authorized to charge the total fees indicated above to my deposit account. <div style="margin-top: 10px;"> <input checked="" type="checkbox"/> (<i>this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account. </div> <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div style="text-align: center;"> 04-0838 <hr style="width: 100%;"/> Deposit Account No. </div> <div style="text-align: center;"> 8/19/03 <hr style="width: 100%;"/> Date (day/month/year) </div> <div style="text-align: center;">  <hr style="width: 100%;"/> Signature </div> </div>	

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

RECEIVED

MAY 30 2003

COLEMAN, Henry, D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
United States of America

Date of mailing (day/month/year) 13 May 2003 (13.05.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference Y03-069	
International application No. PCT/US03/04072	International filing date (day/month/year) 12 February 2003 (12.02.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 15 February 2002 (15.02.02)
Applicant YALE UNIVERSITY et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
15 Febr 2002 (15.02.02)	60/357,354	US	07 Apr 2003 (07.04.03)

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 338.89.75</p>	<p>Authorized officer</p> <p>Gérald PESENTI (Fax : 338 89 75)</p> <p>Telephone No. (41-22) 338 9518</p>
---	---

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

RECEIVED

MAY 22 2003

COLEMAN, Henry, D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
United States of America

Date of mailing (day/month/year) 08 May 2003 (08.05.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference Y03-069	International application No. PCT/US03/04072

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

YALE UNIVERSITY et al (for all designated States except US)
BAKER, David, C. et al (for US)

International filing date : 12 February 2003 (12.02.03)

Priority date(s) claimed : 15 February 2002 (15.02.02)

Date of receipt of the record copy
by the International Bureau : 08 April 2003 (08.04.03)

List of designated Offices :

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ,
EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase - see updated important information (as of April 2002)
- ☒ confirmation of precautionary designations (if applicable)
- ☒ requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.75	Authorized officer: Aurora CENDANA (Fax : 338 89 75) Telephone No. (41-22) 338 9905
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INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office where a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette ("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date (this time limit may not be extended). If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. The Notice of confirmation and payment must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

CERTIFICATE OF MAILING

DT12 Rec'd PCT/PTO 19 JUL 2004

I hereby certify that correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to "Commissioner for Patents, Box PCT, Washington, D.C. 20231" on April 10, 2003.

Harold Hull
Name of person mailing document

Harold Hull
Signature

April 10, 2003
Date

IN THE UNITED STATES RECEIVING OFFICE (RO/US)

APPLICANTS : YALE UNIVERSITY; THE UNIVERSITY OF
TENNESSEE RESEARCH CORPORATION; BAKER, David
C.; CHENG, Yung-Chi, and ZHONG, Sanbao

INT'L APPLICATION NO. : PCT/US03/04072

INT'L FILING DATE : 12 February 2003 (12.02.2003)

TITLE : Novel Tyloindicines and Related Processes, Pharmaceutical
Compositions and Methods

Commissioner for Patents, Box PCT
Washington, D.C. 20231

TRANSMITTAL OF
APPOINTMENT OF AGENT

S I R:

In response to an Invitation to Correct Defects in the International Application (Form PCT/RO/106), mailed 3 April 2003, enclosed herewith please find five (5) Appointment of Agent or Common Representative documents, duly executed by the respective Applicants in the above-identified application.

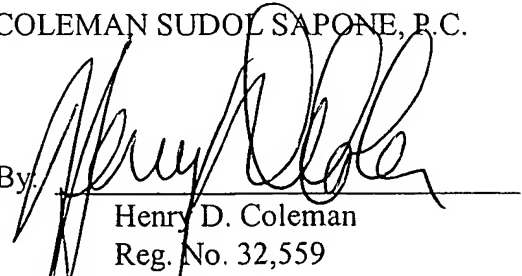
Please charge any fee due in connection with this Transmittal to Deposit Account No. 04-0838. A copy of this Transmittal is enclosed for deposit account charging purposes.

Respectfully submitted,

COLEMAN SUDOL SAPONE, P.C.

Dated: April 10, 2003

By:


Henry D. Coleman
Reg. No. 32,559

714 Colorado Avenue
Bridgeport, CT 06605-1601
(203) 366-3560

10/502074

DT12 Rec'd PCT/PTO 19 JUL 2004

PATENT COOPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

The undersigned applicant hereby appoints as agents:

Henry D. Coleman, Esq.
COLEMAN SUDOL SAPONE, P.C.
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
United States of America

to act on its, their, his, or her behalf before the competent International Authorities in connection with the following international application:

Application Title: Novel Tyloindicines and Related Processes, Pharmaceutical Compositions and Methods
International Application No.: PCT/US03/04072
International Filing Date: 12 February 2003

filed with the United States Receiving Office and to receive payments on its behalf.

APPLICANT: Yale University
NAME: Dorothy K. Robinson
TITLE: Vice-President and General Counsel
ADDRESS: Two Whitney Avenue
New Haven, CT 06511
United States of America

SIGNATURE: Dorothy K. Robinson

DATE: 3/21/03

10/502074

DT12 Rec'd PCT/PTO 19 JUL 2004

PATENT COOPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

The undersigned applicant hereby appoints as agents:

Henry D. Coleman, Esq.
COLEMAN SUDOL SAPONE, P.C.
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
United States of America

to act on its, their, his, or her behalf before the competent International Authorities in connection with the following international application:

Application Title: Novel Tyloindicines and Related Processes, Pharmaceutical Compositions and Methods
International Application No.: PCT/US03/04072
International Filing Date: 12 February 2003


filed with the United States Receiving Office and to receive payments on its behalf.

APPLICANT: The University of Tennessee Research Corporation

NAME: Ann J. Roberson

TITLE: President

ADDRESS: 1534 White Avenue, Suite 403
Knoxville, TN 37996
United States of America

SIGNATURE: 

DATE: 3-11-03

10/502074

RECEIVED 19 JUL 2004

PATENT COOPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

The undersigned applicant hereby appoints as agents:

Henry D. Coleman, Esq.
COLEMAN SUDOL SAPONE, P.C.
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
United States of America

to act on its, their, his, or her behalf before the competent International Authorities in connection with the following international application:

Application Title: Novel Tyloindicines and Related Processes, Pharmaceutical Compositions and Methods
International Application No.: PCT/US03/04072
International Filing Date: 12 February 2003

filed with the United States Receiving Office and to receive payments on its behalf.

APPLICANT: David C. BAKER

ADDRESS: 5708 Glen Cove Drive
Knoxville, TN 37919
United States of America

SIGNATURE: _____

David C. Baker

DATE: MAR 6 2003

10/502074

DT12 Rec'd PCT/PTO 19 JUL 2004

PATENT COOPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

The undersigned applicant hereby appoints as agents:

Henry D. Coleman, Esq.
COLEMAN SUDOL SAPONE, P.C.
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
United States of America

to act on its, their, his, or her behalf before the competent International Authorities in connection with the following international application:

Application Title: Novel Tyloindicines and Related Processes, Pharmaceutical Compositions and Methods
International Application No.: PCT/US03/04072
International Filing Date: 12 February 2003

filed with the United States Receiving Office and to receive payments on its behalf.

APPLICANT: Yung-Chi CHENG

ADDRESS: 961 Baldwin Road
Woodbridge, CT 06525
United States of America

SIGNATURE: Yung-chi Cheng

DATE: 3/1/2003

PATENT COOPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

The undersigned applicant hereby appoints as agents:

Henry D. Coleman, Esq.
COLEMAN SUDOL SAPONE, P.C.
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
United States of America

to act on its, their, his, or her behalf before the competent International Authorities in connection with the following international application:

Application Title: Novel Tyloindicines and Related Processes, Pharmaceutical Compositions and Methods
International Application No.: PCT/US03/04072
International Filing Date: 12 February 2003

filed with the United States Receiving Office and to receive payments on its behalf.

APPLICANT: Sanbao ZHONG

ADDRESS: 18 Redcliffe Avenue, Apt. 2A
Highland Park, NJ 08904
United States of America

SIGNATURE: Sanbao Zhong

DATE: March 3, 2003

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

HENRY D. COLEMAN
COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGEPORT, CONNECTICUT 06605-1601

NOTIFICATION CONCERNING PAYMENT OF PRESCRIBED FEES

(PCT Rules 14, 15 and 16 and Administrative
Instructions, Sections 102bis(c), 304(a) and (b),
323(b), 707(b) and 803)

Date of mailing (day/month/year) 03 APR 03	
Applicant's or agent's file reference Y03-069	PAYMENT DUE see item 3 for time limits
International application No. PCT/US03/04072	International filing date/Date of receipt (day/month/year) 12 Feb 2003
Priority date (day/month/year) 15 Feb 2002	
Applicant YALE UNIVERSITY	

1. The applicant is hereby notified that this receiving Office has received:

- ☒ the payment of all the prescribed fees, and,
 ☐ an overpayment, which will be refunded in due course.
- ☐ no or insufficient payment of the prescribed fees and the applicant is hereby invited to pay the balance due, as summarized under item 2, within the time limit(s) indicated under item 3.

2. Fees and payment calculation:

2,392.00	2,392.00	0.00
Total fees payable	Amount paid	Balance

☐ The details of the calculation are given in the Annex.

3. Time limit(s) for payment and amount(s) payable (Rules 14.1, 15.4 and 16.1(f)):

- ☐ within ONE MONTH from the date of receipt of the international application (for the transmittal fee (if any), the search fee, the basic fee and the designation fee). The amount payable for each fee is the amount applicable on the date of receipt of the international application.
- ☐ within ONE YEAR from the priority date (only for the designation fee and only if this time limit expires later than the above time limit).
 - If the designation fee is paid within one month from the date of receipt of the international application, the amount payable is the amount applicable on that date of receipt.
 - If the designation fee is paid within one year from the priority date but later than one month from the date of receipt of the international application, the amount payable is the amount applicable on the date of payment. The receiving Office should be consulted for the applicable amount.
- ☐ within 16 MONTHS from the priority date (only for the fee for priority document). The applicant's attention is drawn to the fact that the request made by the applicant under Rule 17.1(b) will be considered not to have been made unless the fee is paid within that time limit.

4. Additional observations (if necessary):

- ☐ The search copy will not be transmitted to the International Searching Authority until the search fee is paid (therefore the start of the international search will be delayed) (Rule 23.1(a) and (b)).

Name and mailing address of the receiving Office Assistant Commissioner for Patent, Box PCT Washington, D.C. 20231 Attn:RO/US Facsimile No. 703-305-3230	Authorized officer Valerie Jackson Telephone No. 703-305-3756
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**ANNEX TO FORM PCT/RO/102
CALCULATION OF THE PRESCRIBED FEES**

International application No.
PCT/03/04072

T Transmittal Fee

Prescribed amount: 240.00 **T**
 Amount paid: - 240.00
 Balance: = 0.00

☒ correct amount
☐ overpayment
☐ balance due

S Search Fee

Prescribed amount: 700.00 **S**
 Amount paid: - 700.00
 Balance: = 0.00

☒ correct amount
☐ overpayment
☐ balance due

I International Fee

B Basic Fee

Fixed amount for first 30 sheets: 407.00 **b1**
 $\frac{65}{\text{Number of sheets in excess of 30}} \times \frac{9.00}{\text{Fee per sheet}} = 585.00$ **b2**

Additional component: . . . 400 x $\frac{0.00}{\text{Fee per sheet}} = 0.00$ **b3**

Prescribed amount (b1 + b2 + b3) = 992.00 **B**

D Designation Fee

Amount of designation fee: 88.00
 Number of designation fees payable (maximum 5): x 5
 Prescribed amount = 440.00 **D**

R Reduction where PCT-EASY software is used or where the international application is filed in electronic form (See the PCT Applicant's Guide, Volume I, General Part, for details on the availability of this reduction):

0 **R**

Sub-total (B+D-R): = 1,432.00 **B+D-R**

Prescribed total amount (The amount to be entered at I is the sub-total entered at (B+D-R), except where the applicant is (or all applicants are) entitled to a reduction of 75%, in which case the amount to be entered at I is 25% of the sub-total (B+D-R); certain applicants from certain States are entitled to a reduction of 75% of the international fee; see Notes to the Fee Calculation Sheet as annexed to the Request Form, PCT/RO/101, for details):

1,432.00 **I**

Amount paid: - 1,432.00
 Balance: = 0.00

☒ correct amount
☐ overpayment
☐ balance due

P Fee for priority document

Prescribed amount: 20.00 **P**
 Amount paid: - 20.00
 Balance: = 0.00

☒ correct amount
☐ overpayment
☐ balance due

Additional observations (if necessary):

- ☐ The amount paid for the designation fee covers the following designations: _____
☐ Other (specify): _____

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:
HENRY D. COLEMAN
COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGEPORT, CONNECTICUT 06605-1601

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing (day/month/year) 03 APR 03	
Applicant's or agent's file reference Y03-069	IMPORTANT NOTIFICATION
International application No. PCT/US03/04072	International filing date (day/month/year) 12 Feb 2003
Priority date (day/month/year) 15 Feb 2002	
Applicant YALE UNIVERSITY	
Title of the invention NOVEL TYLOINDICINES AND RELATED PROCESSES, PHARMACEUTICAL COMPOSITIONS AND METHODS	

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

- ☒ was transmitted to the International Bureau on 03 APR 03
- ☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:
- ☐ because the necessary national security clearance has not yet been obtained.
- ☐ because (reason to be specified):

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION

Completed by: VJ

- ☐ Additional license for foreign transmittal not required. This subject matter is covered by a license already granted or the equivalent U.S. national application. Refer to that license for information concerning its scope.
- ☐ License for foreign transmittal not required. 37 CFR. 5.11(e)(1) or 37 CFR 5.11(e)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).
- ☒ Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on 27 Mar 2003 :
- ☐ 37 CFR 5.15(a) ☒ 37 CFR 5.15(b) (date)

Name and mailing address of the receiving Office
Assistant Commissioner for Patent, Box PCT
Washington, D.C. 20231 Attn:RO/US
Facsimile No. 703-305-3230

Authorized officer
Valerie Jackson
Telephone No. 703-305-3756

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

HENRY D. COLEMAN
COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGEPORT, CONNECTICUT 06605-1601

INVITATION TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(i) and 14(1) and Rule 26)

<p>Date of mailing (day/month/year) 03 APR 03</p>	
<p>Applicant's or agent's file reference Y03-069</p>	<p>REPLY DUE within <u>1</u> months/days from the above date of mailing</p>
<p>International application No. PCT/US03/04072</p>	<p>International filing date (day/month/year) 12 Feb 2003</p>
<p>Applicant YALE UNIVERSITY</p>	

1. ☐ The applicant is hereby invited, within the time limit indicated above, to correct, in the International application as filed, the defects specified on the attached:
 - ☒ Annex A
 - ☐ Annex B1 (*text matter of the international application as filed*)
 - ☐ Annex C1 (*drawings of the international application as filed*)
2. ☐ The applicant is hereby invited, within the time limit indicated above, to correct, in the translation of the international application furnished under Rule 12.3 or 12.4, the defects specified on the attached:
 - ☐ Annex A
 - ☐ Annex B2 (*text matter of the translation of the international application*)
 - ☐ Annex C2 (*drawings of the translation of the international application*)

Additional observations (if necessary):

HOW TO CORRECT THE DEFECTS?

Correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. A correction may be stated in a letter only if it is of such a nature that it can be transferred from the letter to the record copy without adversely affecting the clarity and direct reproducibility of the sheet onto which the correction is to be transferred (Rule 26.4).

ATTENTION

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this invitation and any attachments has been sent to the International Bureau

☒ and the International Searching Authority

<p>Name and mailing address of the receiving Office Assistant Commissioner for Patent, Box PCT Washington, D.C. 20231 Attn:RO/US Facsimile No. 703-305-3230</p>	<p>Authorized officer Valerie Jackson Telephone No. 703-305-3756</p>
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The receiving Office has found the following defects in the international application as filed:

1. As to signature* of the international application (Rules 4.15 and 90.4), the request:
- a. ☐ is not signed
 - b. ☐ is not signed by all the applicants
 - c. ☐ is not accompanied by the statement referred to in the check list in Box No. VIII of the request explaining the lack of the signature of an applicant for the designation of the United States of America
 - d. ☒ is signed by what appears to be an agent/common representative but:
 - ☒ the international application is not accompanied by a power of attorney appointing him
 - ☐ the power of attorney accompanying the international application was not signed by all the applicants
 - e. ☐ other (specify):

A SIGNED POWER OF ATTORNEY IS NEEDED FROM ALL LISTED APPLICANT/INVENTORS

* All applicants must sign, including inventors if they are also applicants (e.g. where the United States of America is designated).

2. As to indications concerning the applicant, the request (Rules 4.4 and 4.5):

- a. ☐ does not properly indicate the applicant's name (specify):
- b. ☐ does not indicate the applicant's address
- c. ☐ does not properly indicate the applicant's address (specify):
- d. ☐ does not indicate the applicant's nationality
- e. ☐ does not indicate the applicant's residence
- f. ☐ other (specify):

3. As to the language of certain elements of the international application, other than the description and claims (Rules 12.1(c) and 26.3ter(a) and (c)):

- a. ☐ the request is not in a language of publication accepted by this receiving Office; (the) language(s) accepted by this receiving Office is/are:
- b. ☐ the text matter of the drawings is not in the language in which the international application is to be published, which is:
- c. ☐ the abstract is not in the language in which the international application is to be published, which is:

4. The title of the invention:

- a. ☐ is not indicated in Box No. I of the request (Rule 4.1(a))
- b. ☐ is not indicated at the top of the first sheet of the description (Rule 5.1(a))
- c. ☐ as appearing in Box No. I of the request is not identical with the title heading the description (Rule 5.1(a))

5. As to the abstract (Rule 8):

- ☐ the international application does not contain an abstract

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF RECEIPT
OF SEARCH COPY

(PCT Rule 25.1)

To:

HENRY D. COLEMAN
COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGEPORT, CONNECTICUT 06605-1601

Date of mailing
(day/month/year)

03 APR 03

Applicant's or agent's file reference

Y03-069

IMPORTANT NOTIFICATION

International application No.

PCT/US03/04072

International filing date (day/month/year)

12 Feb 2003

Priority date (day/month/year)

15 Feb 2002

Applicant

YALE UNIVERSITY

1. Where the International Searching Authority and the receiving Office are not the same Office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the receiving Office are the same Office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

03 APR 03

(date of receipt).

2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing in computer readable form.

3. Time limit for establishment of international search report

The applicant is informed that the time limit for establishing the international search report is 3 months from the date of receipt indicated above or 9 months from the priority date, whichever time limit expires later.

4. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the receiving Office.

Name and mailing address of the ISA/

Assistant Commissioner for Patent, Box PCT
Washington, D.C. 20231 Attn: RO/US

Facsimile No. 703-305-3230

Authorized officer

Valerie Jackson

Telephone No. 703-305-3756

TO: HENRY D. COLEMAN COLEMAN SUDOL SAPONE, P.C. 714 COLORADO AVENUE BRIDGEPORT, CONNECTICUT 06605-1601	UNITED STATES DESIGNATED/ELECTED OFFICE (DO/US)
	NOTIFICATION OF STATUS OF REQUIREMENTS UNDER 35 U.S.C. 371
	DATE OF MAILING (day/month/year) 03 APR 03
FILE REFERENCE Y03-069	

IDENTIFICATION OF INTERNATIONAL APPLICATION		
International application No. PCT/US03/04072	International filing date (day/month/year) 12 Feb 2003	Priority Date Claimed 15 Feb 2002
Applicant for DO/EO/US CHENG, YUNG-CHI		

NOTIFICATION

The applicant is hereby advised that the U.S. Patent and Trademark Office in its capacity as ☒ Designated Office ☐ Elected Office has received following items as of the date of mailing indicated above.

1. ☐ U.S. Nation fee [35 U.S.C 371 (c) (1)]
 2. ☐ Oath of declaration [35 U.S.C 371 (c) (4)]
 3. ☒ Copy of International application as [35 U.S.C 371 (c) (2)]
 4. ☐ Translation of Application [35 U.S.C 371 (c) (2)]
 5. ☐ Amendments under PCT Article 19 [35 U.S.C 371 (c) (3)]
 6. ☐ Translation of PCT Article 19 Amendments [35 U.S.C 371 (c) (3)]
 7. ☐ Search Report or Declaration under PCT Article 17(2) [35 U.S.C 371 (a)]
 8. ☐ International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(b) [35 U.S.C 371 (a)]
 9. ☐ Translation of Annexes to the International Preliminary Examination Report under PCT Article 36(3)(b) [35 U.S.C 371 (c) (5)]
 10. ☐ Other items received:

☐ Assignment Document ☐ Prior Art Statement ☐ Preliminary Amendment
- A. ☐ Requirements for U.S. National processing have been met. Processing will commence
- ☐ at the expiration of the applicable time limit under either

☐ PCT Article 22 [35 U.S.C 371 (b)] or
☐ PCT Article 39 [35 U.S.C 371 (b)]

☐ on the date indicated below under the provisions of 35 U.S.C 371 (f)

U.S. NATIONAL SERIAL#

DATE UNDER 35 U.S.C. 102(e)

DATE OF COMMENCEMENT
OF NATIONAL PROCESSING

All correspondence submitted after the date of commencement of U.S. National processing indicated above should refer to the U.S. National Serial Number and the appropriate U.S. National processing organization of Officer.

- B. ☐ As the above identified application has been accepted for U.S. National processing under the provision of 35 U.S.C. 371 (f) before expiration of the applicable time limit under ☐ PCT Article 22 ☐ PCT Article 39, applicant is reminded that
- ☐ Amendments under PCT Article 19 and/or
☐ the International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3) (a), and (b) and any translation thereof, if applicable, must be submitted to the Patent and Trademark Office as soon as they are available.

International application No. PCT/US03/04	International filing date 12 Feb 2003	Priority Date Claimed 15 Feb 2002
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C. ☒ In order that U.S. National processing may begin, certain items must be received by the DO/EO/US by the expiration of applicable time limit under

☒ PCT Article 22 or
☒ PCT Article 39.

Specifically:

- ☒ 1. U.S. National Fee
- ☒ 2. Oath or Declaration
- ☐ 3. Copy of Application
- ☐ 4. Translation of application
- ☒ 5. Amendments under PCT Article 19, if any
- ☐ 6. Translation of PCT Article 19 Amendments, if applicable
- ☐ 7. Search Report or PCT Article 17(2) declaration
- ☐ 8. International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(a), if applicable
- ☐ 9. Translation of Annexs to the International Preliminary Examination Report under PCT Article 36(3)(b), if applicable

***THE ABOVE CHECK ITEMS MUST BE TIMELY RECEIVED TO AVOID ABANDONMENT OF THE APPLICATION.
[35. U.S.C. 371(d)]***

D. Further information for the applicant:

This is only a reminder.

UNITED STATES DESIGNATED/ELECTED OFFICE	
Address Only: Assistant Commissioner for Patent, Box PCT Washington, D.C. 20231 Attn:RO/US	Authorized Officer Valerie Jackson 703-305-3756

PCT INTERNATIONAL APPLICATION TRANSMITTAL LETTER - DATE: February 12, 2003	
REGARDING THE INTERNATIONAL APPLICATION OF YALE UNIVERSITY et al.	DOCKET NO: Y03-069
ENTITLED: NOVEL TYLOINDICINES AND RELATED PROCESSES, PHARMACEUTICAL COMPOSITIONS AND METHODS	

Certification under 37 C.F.R. 1.10 (if applicable)

EL 890537389 US

"Express Mail" mailing number

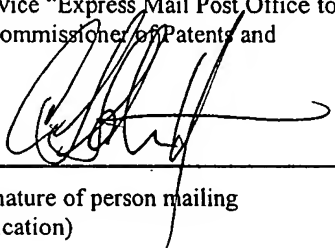
February 12, 2003

Date of Deposit

I hereby certify that this application is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Curtis L. Schrandt

(Typed or printed name of person
mailing application)



(Signature of person mailing
application)

To the United States Receiving Office (RO/US):

Accompanying this transmittal letter is the above-identified International application, including a completed Request form (PCT/RO/101). Please process the application according to the provisions of the Patent Cooperation Treaty.

The following requests are made of the RO/US:

- ☒ PREPARATION AND TRANSMITTAL OF CERTIFIED COPY OF PRIORITY DOCUMENTS - Please prepare and transmit to the International Bureau a certified copy of the United States Origin priority documents identified in Box VI of the Request form (37 C.F.R. 1.451).

To cover the cost of copy preparation and certification (37 C.F.R. 1.19(a)(3) and (b)(1)),

- ☒ a check in the amount of \$ 2137.00 is attached to this transmittal letter, which includes the amount of \$15.00 for the cost of the certified copy.

- ☐ the RO/US is hereby authorized to charge the following to deposit account no.: _____

The appropriate Search fee for the above-named Authority is indicated on the Fee Calculation Sheet (PCT/RO/101 Annex).

- ☐ SUPPLEMENTAL SEARCH FEES (ONLY WHEN ISA/US CONDUCTS THE INTERNATIONAL SEARCH.) Please charge any Supplemental Search fees that may be required by the United States International Searching Authority to deposit

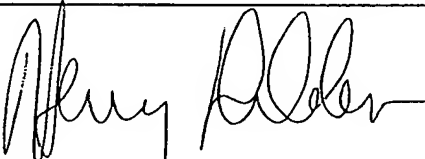
account no. _____

I understand that this authorization is subject to my oral confirmation thereof in each instance and that it in no way limits my right to submit a protest against payment of the Supplemental Search fees but is merely an administrative aid to assure that the ISA/US may timely complete the Search Report.

NOTE: SUPPLEMENTAL SEARCH FEES FOR ISA/EP ARE PAYABLE DIRECTLY TO THE EUROPEAN PATENT OFFICE.

3. ☒ DISCLOSURE INFORMATION - In order to assist in screening the accompanying International application for purposes of determining whether a license for foreign transmittal should and could be granted, the following information is supplied:
- A ☐ There is no prior filed application relating to this invention.
- B ☒ There are prior applications* serial number 60/357,354 filed on Feb. 15, 2002
which contains subject matter that is
1. ☐ Substantially identical to that of the accompanying International application.
2. ☒ Less than that of the accompanying International application. The additional subject matter of the International application
appears on page(s) _____ and lines _____
3. ☐ more than that of the accompanying International application.
- C ☐ Disclosure information cannot be covered by the language of points 4A or 4B above due to the involvement of several prior applications or for other reasons. A separate sheet on which the disclosure information is explained is attached to this transmittal letter.
4. ☒ REQUEST FOR FOREIGN TRANSMITTAL LICENSE - According to the provisions of 35 U.S.C. 184 and 37 C.F.R. 5.11, a license to transmit the accompanying International application to foreign agencies or international authorities is hereby requested.

*Priority is not claimed, unless all necessary information is listed in Box VI of the Request form (PCT/RO/101).

Signer is the:	Name of Signer: Henry D. Coleman
<input type="checkbox"/> Applicant	
<input type="checkbox"/> Common Representative	
<input checked="" type="checkbox"/> Attorney or Agent, Reg. No: 32,559	
	Signature:

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

for receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file
reference:
(if desired)(12 characters maximum)

Y03-069

Box No. I TITLE OF INVENTION

NOVEL TYLOINDICINES AND RELATED PROCESSES, PHARMACEUTICAL COMPOSITIONS AND METHODS

Box No. II APPLICANT

Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

Yale University
Two Whitney Avenue
New Haven, Connecticut 06511
United States of America

☐ This person is also inventor

Telephone No.
(203) 432-5546

Facsimile No.
(203) 432-5449

Teleprinter No.

State (i.e. country) of Nationality: US

State (i.e. country) of Residence: US

This person is
applicant for the
purposes of:



all designated
States



all designated States except
the United States of
America



the United States
of America only



the states indicated
in the supplemental
box

Box No. III FURTHER APPLICANT(S) AND/OR FURTHER INVENTOR(S)

Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

University of Tennessee Research Corporation
1534 White Avenue, Suite 403
Knoxville, TN 37996
United States of America

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only (if this check-box
is marked, do not fill in below)

State (i.e. country) of nationality: US

State (i.e. country) of residence: US

This person is
applicant for the
purposes of:



all designated
States



all designated States except
the United States of
America



the United States
of America only



the states indicated
in the supplemental
box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:



agent



common representative

Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

Henry D. Coleman
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
United States of America

Telephone No. (203) 366-3560

Facsimile No. (203) 335-6779

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

BAKER, David C.
5708 Glen Cove Dr.
Knoxville, TN 37919
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below)

State (i.e. country) of nationality: US

State (i.e. country) of residence: US

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the states indicated in the supplemental box

Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

CHENG, Yung-Chi
961 Baldwin Rd.
Woodbridge, CT 06525
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below)

State (i.e. country) of nationality: US

State (i.e. country) of residence: US

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the states indicated in the supplemental box

Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

ZHONG, Sanbao
18 Redcliffe Avenue, Apt. 2A
Highland Park, NJ 08904
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below)

State (i.e. country) of nationality: CN

State (i.e. country) of residence: US

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the states indicated in the supplemental box

Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the states indicated in the supplemental box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Form PCT/RO/101 (continuation sheet)

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda | <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> OM Oman |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> PH Philippines |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> JP Japan | |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> KR Republic of Korea | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> BZ Belize | <input checked="" type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> CH & LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> LK Sri Lanka | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> LR Liberia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> CO Colombia | <input checked="" type="checkbox"/> LS Lesotho | <input checked="" type="checkbox"/> TN Tunisia |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> LT Lithuania | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> LU Luxembourg | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> LV Latvia | |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> MA Morocco | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> MD Republic of Moldova | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> MG Madagascar | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> DZ Algeria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> EC Ecuador | <input checked="" type="checkbox"/> MN Mongolia | |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> MW Malawi | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> MX Mexico | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> MZ Mozambique | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> NO Norway | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> GD Grenada | | <input checked="" type="checkbox"/> ZM Zambia |
| <input checked="" type="checkbox"/> GE Georgia | | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ all other PCT member states
- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM☒

The priority of the following application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of Filing (only for regional or international application)
item (1) US	February 15, 2002	60/357,354	
item (2)			
item (3)			

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): (1)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA):

ISA/USPTO

Earlier Search

Country(or regional Office):

Date (day/month/year):

Number:

Box No. VIII CHECK LIST

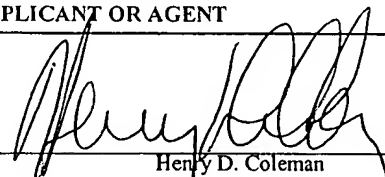
This international application contains the following number of sheets:

1. request : 4 sheets
 2. description : 44 sheets
 3. claims : 19 sheets
 4. abstract : 1 sheets
 5. drawings : 27 sheets
 Total : 95 sheets

This international application is accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. <input type="checkbox"/> separate signed power of attorney | 5. <input checked="" type="checkbox"/> fee calculation sheet |
| 2. <input type="checkbox"/> copy of general power of attorney | 6. <input type="checkbox"/> separate instructions concerning deposited micro-organisms |
| 3. <input type="checkbox"/> statement explaining lack of signature | 7. <input type="checkbox"/> nucleotide and/or amino acid sequence listing (diskette) |
| 4. <input type="checkbox"/> priority document(s) | 8. <input type="checkbox"/> other (specify) |

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

 Henry D. Coleman

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA/	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT

FEE CALCULATION SHEET

Annex to the Request

International application No.

Applicant's or
agent's file
reference:

Y03-069

Date Stamp of the receiving Office

Applicant: Yale University et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE. 240 T

2. SEARCH FEE. 450 S

International search to be carried out by USPTO

3. INTERNATIONAL FEE

Basic Fee

The international application contains 95 sheets.

first 30 sheets. 407 b₁

$$\begin{array}{rcl} 65 & \times & 9 \\ \hline & & 585 \end{array}$$

remaining sheets
additional amount

Add amounts entered at b₁ and b₂ and enter total at B. 992 B

Designation Fees

The international application contains designations.

$$\begin{array}{rcl} 5 & \times & 88 \\ \hline & & 440 \end{array}$$

number of designation fees payable (maximum 6)
amount of designation fee

Add amounts entered at B and D and enter total at I. 1432 I

4. FEE FOR PRIORITY DOCUMENT. 15 P

5. TOTAL FEES PAYABLE

Enter amounts entered at T, S, I, and P, and enter total in the TOTAL box.

2137
TOTAL☐ The designation fees are not paid at this time

MODE OF PAYMENT

☐ authorization to charge deposit account
☒ cheque
☐ postal money order

☐ bank draft
☐ cash
☐ revenue stamps

☐ coupons
☐ other (specify)

DEPOSIT ACCOUNT AUTHORIZATION

The RO/ US

☐ is hereby authorized to charge the total fees indicated above to my deposit account.☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

04-0838

12 February 2003

Deposit Acct. No.

Date (day/month/year)

Signature